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Anterior cingulate volume reductions in abstinent adolescent and young adult cannabis users: Association with affective processing deficits

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1. Introduction

Cannabis use is increasing amongst young adults, with 20% using within the past month (Johnston et al., 2016). Adolescents and emerging adults may be especially vulnerable to the negative effects of cannabis use due to the substantial neurodevelopment occurring during this period (Jacobus and Tapert, 2014; Lisdahl et al., 2013; Lisdahl et al., 2014). Cannabis use has a high rate of comorbidity with affective disorders that often emerge during adolescence and young adulthood (Agrawal et al., 2011; Dorard et al., 2008; Wittchen et al., 2007). A possible mechanism underlying psychiatric comorbidities and mood symptoms in young cannabis users is abnormalities in the affective neural network, resulting in deficits in affective processing. One commonality of many disorders (including anxiety, depression, bipolar disorder, and psychosis) comorbid with cannabis use is a deficit in facial emotion processing (Bourke et al., 2010; Mogg et al., 2000; Morris et al., 2009; Samame, 2013), which is a critical aspect of functioning in human social networks (Phillips et al., 2003).

Cannabis use has been associated with abnormal facial emotion processing. Cannabis users are less accurate in recognizing and discriminating between emotions (Bayrakci et al., 2015; Hindocha et al., 2014; Huijbregts et al., 2014). An additional consideration is that cannabis users' accuracy in identifying emotions depends upon the intensity at which the emotion is displayed. Yet, studies probing the importance of emotion intensity have yielded mixed findings. One study concluded that cannabis users had more difficulty identifying more subtle emotions (Platt et al., 2010), while another reported that cannabis users were less accurate than controls only in recognizing more overt, unambiguous emotions (Hindocha et al., 2014). Another study found emotion recognition deficits only in more frequent and recent cannabis users (Huijbregts et al., 2014). Functional magnetic resonance imaging (MRI) studies have extended this behavioral work. During facial emotion tasks, cannabis use has been associated with abnormal anterior cingulate cortex (ACC) and amygdala activation (Cornelius et al., 2010; Gruber et al., 2009; Spechler et al., 2015).

Facial processing is complex, recruiting a distributed network of visual, limbic, temporoparietal, and prefrontal areas, as well as the cerebellum (Fusar-Poli et al., 2009b; Haxby et al., 2000; Ishai et al., 2004, 2005; Kesler-West et al., 2001; Said et al., 2011). Haxby et al. (2000) model proposes a core system of face perception, consisting of the fusiform gyrus and superior temporal sulcus. In addition to this core system of facial processing, an extended system consists of a distributed network of regions that are recruited to derive meaning from facial expressions, including facial emotion (Haxby et al., 2000). This extended system includes areas such as the medial prefrontal cortex (PFC) (Fusar-Poli et al., 2009b; Kesler-West et al., 2001), orbital frontal cortex (OFC) (Ishai et al., 2005), inferior frontal gyrus (Ishai et al., 2005; Kesler-West et al., 2001), ACC (Wu et al., 2016), amygdala (Fusar-Poli et al., 2009b; Gur et al., 2002; Morris et al., 1996), hippocampus (Gur et al., 2002; Ishai et al., 2005), and cerebellum (Fusar-Poli et al., 2009b). During processing of emotional versus neutral unfamiliar faces, the entire face perception network is recruited more intensely (Ishai et al., 2004, 2005; Pessoa et al., 2002). Thus, all regions in the network are considered important in facial emotion recognition.

Cannabis use has been associated with structural differences in regions associated with emotional face processing. Cannabis users have exhibited structural abnormalities in volume and thickness within cortical regions including the frontal cortex (medial OFC (mOFC), lateral OFC (lOFC), ACC), temporal lobe, and fusiform gyrus (Battistella et al., 2014; Cheetham et al., 2012; Churchwell et al., 2010; Chye et al., 2017; Epstein and Kumra, 2015; Jacobus et al., 2014; Jarvis et al., 2008; Koenders et al., 2016; Lisdahl et al., 2016; Lopez-Larson et al., 2011; Mashhoon et al., 2015; Mata et al., 2010; Medina et al., 2009; Price et al., 2015; Thames et al., 2017). Cannabis use has also been linked with volume differences in subcortical regions such as the amygdala, hippocampus, and cerebellum (Ashtari et al., 2011; Battistella et al., 2014; Cousijn et al., 2012; Demirakca et al., 2011; Gilman et al., 2014; Jarvis et al., 2008; Koenders et al., 2016; Matochik et al., 2005; McQueeny et al., 2011; Medina et al., 2010; Medina et al., 2007; Nurmedov et al., 2015; Pagliaccio et al., 2015; Schacht et al., 2012; Solowij et al., 2013; Yucel et al., 2008). Typically, cannabis users, compared to non-users, have smaller volumes in these brain regions, though some studies in younger adolescent samples have found larger volumes in cannabis users (e.g., McQueeny et al., 2011; Medina et al., 2009, 2010). Despite the aforementioned literature, some studies have reported null findings for each of these brain regions (e.g., Tzilos et al.,

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2005; Weiland et al., 2015), suggesting a greater need to understand individual differences, such as gender, moderating the relationship between cannabis use and brain structure.

Males and females recruit different networks while processing emotional faces (Filkowski et al., 2017; Kempton et al., 2009; Whittle et al., 2011). Further, female affective circuitry may be more susceptible to the negative effects of cannabis use (for review, see Crane et al., 2013). Within adolescent female compared to male rats, increased cannabinoid receptor-1 (CB1) downregulation is observed in fronto-limbic regions (Rubino et al., 2008). Additionally, relative to males, female rats exposed to tetrahydrocannabinol (THC), the main psychoactive component in cannabis, are more vulnerable to its anxiety and depression producing properties (Rubino et al., 2008). In humans, female cannabis users have exhibited functional disadvantages associated with differences in PFC, lOFC, and amygdala volumes compared to their male counterparts (Chye et al., 2017; McQueeny et al., 2011; Medina et al., 2009). Thus, cannabis-using females may process facial emotions differently from male users, and this may be related to underlying brain structure in frontolimbic areas.

Yet, to date, no study has investigated the relationship between brain structure, gender, and facial affective processing in abstinent cannabis users. The current study is novel in its focus on cannabis use and brain structure in facial emotion processing regions. More specifically, it is unclear in the existing literature if abnormal brain structure in cannabis users has functional consequences related to facial emotion processing. To address this gap in the literature, the primary aim of the current study was to examine the relationship between cannabis use and brain volumes in regions underlying facial emotion processing. We also investigated whether gender moderated this relationship. We hypothesized that cannabis use would be associated with reduced volumes, and that females would exhibit the strongest relationship between cannabis use and reduced volumes. For our secondary aim, we assessed whether differences in brain volumes associated with cannabis use and cannabis x gender interaction were related to deficits in facial emotion processing. We expected that brain volume would be related to poorer facial emotion processing within the cannabis-using group.

2. Methods

2.1. Participants

Participants included 20 cannabis using and 35 non-using individuals (28 males and 27 females), ages 16–26 years, from a larger neuroimaging study (PI: Lisdahl, NIH R01 DA030354). Individuals were recruited through flyers posted in the community. In the current analysis, cannabis users were required to have at least 40 uses in the past year and at least 50 lifetime uses. Non-users were required to have fewer than or equal to 5 lifetime uses. Individuals were excluded for left-handedness, MRI contraindications, birth complications, birth < 33 weeks gestation, neurological disorders, head trauma with > 2 min loss of consciousness, learning or intellectual disability, vision or hearing impairments, major health problems, independent DSM-IV-TR psychological disorder, current use of psychotropic medication, use of more than 10 cigarettes per day, heavy other drug use (> 25 lifetime uses of non-cannabis drugs), pregnancy, and failure to demonstrate abstinence from all substances on the day of MRI scanning (as indicated by blood alcohol concentration of > 0.000, positive urine toxicology, and/or continuous sweat patch testing).

2.2. Design and procedure

The Institutional Review Boards at the University of Wisconsin-Milwaukee and the Medical College of Wisconsin (MCW) approved all aspects of this study. Interested individuals from the community underwent phone screening to determine eligibility, during which comprehensive substance use history (lifetime) was obtained with the

Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998; Stewart and Brown, 1995). Information regarding youth psychiatric history was gathered via a Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) semi-structured interview (Sheehan et al., 1998) administered to both participants and parents.

Informed consent was obtained from eligible participants prior to the study. All participants (cannabis users and non-users) underwent three weeks of monitored abstinence prior to completing the affective processing tasks (Session #4) and MRI scan (Session #5), which occurred 24–48 h apart. At weekly sessions (Sessions #1, 2, 3) during the three weeks prior to the affective processing tasks and MRI, participant abstinence was evaluated using urine toxicology (One Step Drug Screen Test Dip Card Panel; Innovacon, Inc., San Diego, CA) and continuous sweat toxicology (PharmChek Drugs of Abuse Patch; PharmChem Inc., Fort Worth, TX), which measured levels of THC and other substances. In addition, at each session, participants underwent breathalyzer testing (Alco-Sensor IV; Intoximeters, Inc., St. Louis, MO) for recent alcohol use.

2.3. Measures

2.3.1. Demographic information

Participants completed a background questionnaire outlining demographic variables including age, gender, ethnicity, and education.

2.3.2. Substance use

During each session, participants reported the last instance of any substance use. In addition, participants completed the Timeline Follow Back (TLFB; Sobell and Sobell, 1992). This is a highly reliable and valid measure of past year substance use, using holidays and other memory cues. As part of completing the TLFB, participants were asked to report the quantity of specific substances used on each day during the past year. Substance use was measured in standard units (e.g., joints for cannabis). Lifetime and past 3-month substance use was measured using the CDDR.

2.3.3. Affective processing

During Session #4, participants completed an affective battery (PennCNP: https://penncnp.med.upenn.edu/about.html) containing three tasks of interest to the current analysis: Emotion Recognition, Emotion Discrimination, and Emotional Acuity tasks. In Emotion Recognition, participants were presented with a series of faces and instructed to identify which emotion each face was expressing. Possible answer choices included happy, sad, anger, fear, and no emotion. The facial stimuli are described by Gur et al. (2002) and Pinkham et al. (2008). In the Emotion Discrimination task, participants were presented with one pair of faces for each trial. Each pair of faces contained two pictures of the same individual, with or without a subtle (computer-generated) change in facial expression, which possibly indicated a difference in intensity between the two facial emotions. During each trial, the participant decided which picture expressed the specified emotion (happy or sad) more intensely, or whether they were equal. In the Emotional Acuity task, individual faces were randomly presented, and participants were instructed to rate the facial expression's emotional valence on a 7-point scale: very sad, moderately sad, somewhat sad, neutral, somewhat happy, moderately happy, or very happy. Facial stimuli for the Emotion Discrimination and Emotional Acuity tasks are described by Erwin et al. (1992).

2.4. MRI data acquisition and pre-processing

2.4.1. MRI acquisition

Participants were scanned on a 3T scanner (GE Healthcare, Waukesha, WI) at MCW. Structural image acquisition took approximately 15 min. A T1-weighted, 3-D anatomical brain scan was obtained with spoiled gradient-recalled at steady-state (SPGR) pulse sequence

(TR = 8.2 ms, TE = 3.4 s., TI = 450 and flip angle of 12°). The in-plane resolution of the anatomical images was 256 × 256 with a square field of view (FOV) of 240 mm. Slice thickness was 1 mm, with 150 slices acquired.

2.4.2. MRI pre-processing

Structural images were processed using FreeSurfer 5.3′s semi-automated processing stream (http://surfer.nmr.mgh.harvard.edu). All T1-weighted 3D anatomical datasets underwent motion correction, non-parametric non-uniform intensity normalization, Montreal Neurologic Institute transformation, removal of non-brain materials, and skull-stripping. This was followed by whole-brain segmentation of white and gray matter and calculation of cortical and subcortical volumes (Fischl et al., 2002, 2004), using the Desikan-Killiany atlas (Desikan et al., 2006) in FreeSurfer. All automated FreeSurfer steps were inspected for processing errors, and manual edits were made as needed. For each case, automatic segmentation and parcellation masks were manually edited for accuracy, using multiple views for visual inspection. While FreeSurfer's atlases include several regions, only volumes of select cortical and subcortical regions known to be associated with facial emotion processing were included in the current analysis.

2.5. Data analysis

All analyses were conducted using Statistical Package for the Social Sciences (SPSS). Demographic and other drug use was examined using Analysis of Variance (ANOVA) and Chi-Square analyses to detect differences between groups. Variables that either differed between groups or have known relationships with affective processing or brain structure were statistically controlled for in the regressions. Covariates included gender, past year alcohol use, past year nicotine use, and intracranial volume (ICV).

2.5.1. Principal components analysis (PCA) for emotional processing tasks

Due to the mixed findings regarding cannabis use and facial emotion processing, many variables were of potential interest to the current study. In order to minimize the number of individual variables investigated, and therefore the number of tests run, we conducted principal components analyses (PCA) to identify the most salient constructs for investigation. We conducted three PCAs to extract components from each of the Emotion Recognition, Emotion Acuity, and Emotion Discrimination tasks. Accuracy and response time variables were selected for each task and entered into PCA (Tables 1–3).

2.5.2. Primary analysis

Across all 55 cannabis users and non-users, standard entry regression with two blocks (including appropriate covariates) was used to determine the relationship between past year cannabis use, cannabis x gender interaction, and brain structure. Dependent variables included bilateral mOFC, lOFC, Pars triangularis (subregion of inferior frontal gyrus), superior temporal, fusiform, rostral ACC (rACC), caudal ACC

(cACC), amygdala, hippocampus, and cerebellum volumes. Main effects and covariates were entered into the first block of the regressions; interaction variables were also included in the second block. In order to assess if any participants disproportionately influenced significant regression models, DFBETA analyses were conducted for past year cannabis use and cannabis × gender interactions. DFBETA analyses determined that no outliers were present. False Discovery Rate (FDR) corrections (Benjamini and Hochberg, 1995 method) examining the relationships of cannabis and cannabis x gender interactions with brain volume variables were run separately for subcortical and cortical variables within each brain hemisphere (R/L). Additionally, f^2 was used to assess effect sizes for multiple regression analyses (small = 0.02–0.14, medium = 0.15–0.34, and large = > 0.35) (Cohen et al., 1988).

2.5.3. Secondary analysis: brain-behavior relationships

We conducted brain-behavior analyses on brain regions that were significantly associated with past year cannabis use or cannabis × gender interactions. For significant regions, we ran Pearson correlations to determine whether brain abnormalities were related to emotional processing accuracy, within the cannabis-using group. For all analyses, significance was determined if $p < 0.05$. DFBETA analyses determined that no participants disproportionately influenced significant correlation models. FDR corrections were run separately for each of the three affective processing tasks, for each significant brain region.

3. Results

3.1. Demographic & drug use information (Table 4)

3.1.1. Cannabis

ANOVAs and chi-square tests revealed no significant difference between cannabis users and non-users in age ($F_{(1,53)} = 2.25$, $p = 0.14$), race ($\chi^2(5) = 5.80$, $p = 0.33$), ethnicity ($\chi^2(2) = 1.26$, $p = 0.53$), gender ($\chi^2(1) = 1.04$, $p = 0.31$), education ($F_{(1,53)} = 0.20$, $p = 0.65$), and reading ability ($F_{(1, 53)} = 0.67$, $p = 0.42$). Cannabis users and non-users significantly differed on measures of lifetime cannabis use ($F_{(1,53)} = 26.97$, $p = 0.000003$), number of days per month of cannabis use in the past three months ($F_{(1,53)} = 120.71$, $p < 0.000001$), past year cannabis use ($F_{(1,53)} = 41.05$, $p < 0.000001$), past year alcohol use ($F_{(1,53)} = 26.29$, $p = 0.000004$), and past year nicotine use ($F_{(1,53)} = 8.46$, $p = 0.005$).

3.1.2. Gender

ANOVAs and chi-square tests revealed no significant difference between males and females in age ($F_{(1,53)} = 0.06$, $p = 0.80$), race ($\chi^2(5) = 8.74$, $p = 0.12$), ethnicity ($\chi^2(2) = 3.77$, $p = 0.15$), education ($F_{(1,53)} = 0.03$, $p = 0.86$), reading ability ($F_{(1,53)} = 2.0$, $p = 0.16$), age of onset of weekly cannabis use ($F_{(1,18)} = 0.40$, $p = 0.85$), length of cannabis abstinence ($F_{(1,20)} = 0.69$, $p = 0.42$), lifetime cannabis use

Table 1

Emotion recognition principal components analysis factor loadings.

Affective variable	Component labels			
	Recognition time	Sad correct	Happy correct	Anger correct
Anger Correct	−0.021	−0.001	−0.027	**0.939**
Fear Correct	−0.433	0.554	0.298	0.289
Sad Correct	0.096	**0.913**	−0.063	−0.078
Happy Correct	0.030	0.001	**0.964**	−0.025
Anger Correct Median Response Time	**0.659**	−0.310	0.106	0.280
Fear Correct Median Response Time	**0.822**	−0.058	−0.303	−0.049
Happy Correct Median Response Time	**0.649**	−0.116	−0.078	−0.122
Neutral Correct Median Response Time	**0.775**	0.366	0.120	0.110
Sad Correct Median Response Time	**0.823**	0.077	0.164	−0.097

Note. Bolded values denote variable loadings of ≥ 0.6. All response times in milliseconds.

Table 2
Emotional acuity principal components analysis factor loadings.

Affective variable	Component labels Acuity time	Acuity neutral	Acuity intensity
Total Correct	−0.131	**0.894**	0.416
Very Happy Correct	−0.125	−0.107	**0.807**
Happy Neutral Correct	−0.122	**0.854**	−0.124
Neutral Correct	−0.214	**0.923**	−0.082
Sad Neutral Correct	−0.190	**0.755**	0.050
Very Sad Correct	0.209	0.163	**0.650**
Correct Trials Median Response Time	**0.962**	−0.189	0.085
Correct Very Happy Trials Median Response Time	**0.804**	0.071	−0.180
Correct Happy Neutral Trials Median Response Time	**0.836**	−0.190	−0.017
Correct Neutral Trials Median Response Time	**0.914**	−0.262	0.083
Correct Sad Neutral Trials Median Response Time	**0.865**	−0.143	0.183
Correct Very Sad Trials Median Response Time	**0.646**	−0.199	0.016

Note. Bolded values denote variable loadings of ≥0.6. All response times in milliseconds. The "Acuity Neutral" component has high loadings from variables indicating total correct identifications as well as correct identification of more neutral emotions. The "Acuity Intensity" component has high loadings from variables indicating correct identification of more extreme or intense emotions.

Table 3
Emotion discrimination principal components analysis factor loadings.

Affective variable	Component labels Discrimination time	Discrimination correct
Total Correct	0.091	**0.991**
Happy Trials Correct	0.147	**0.886**
Sad Trials Correct	−0.008	**0.856**
Correct Happy Trials Median Response Time	**0.910**	−0.001
Incorrect Happy Trials Median Response Time	**0.732**	0.387
Correct Sad Trials Median Response Time	**0.882**	−0.014
Incorrect Sad Trials Median Response Time	**0.859**	0.182
Total Correct Trials Median Response Time	**0.975**	−0.007

Note. Bolded values denote variable loadings of ≥0.6. All response times in milliseconds.

($F(1,53) = 1.81$, $p = 0.19$), number of days per month of cannabis use in the past three months ($F(1,53) = 1.21$, $p = 0.28$), past year cannabis use ($F(1,53) = 0.97$, $p = 0.33$), past year alcohol use, ($F(1,53) = 2.46$, $p = 0.12$), and past year nicotine use ($F(1,53) = 2.60$, $p = 0.11$).

3.2. Principal components analysis

Three PCAs with varimax rotation were conducted to reduce variables from the each of the tasks (Emotion Recognition, Acuity, and Discrimination) in the PennCNP affective battery. Variables with loadings ≥ 0.6 were considered to define a component.

3.2.1. Emotion recognition

For the Emotion Recognition task, nine variables yielded four components meeting Kaiser's criterion (eigenvalues >1) (Table 1): Recognition Time (33.42% of variance), Sad Correct (15.48% of variance), Happy Correct (13.03% of variance), and Anger Correct (12.10% of variance).

3.2.2. Emotional acuity

For the Emotional Acuity task, twelve variables yielded three components meeting Kaiser's criterion. Components included Acuity Time (37.04% of variance), Acuity Neutral (26.61% of variance), and Acuity Intensity (11.27% of variance) (Table 2).

3.2.3. Emotion discrimination

For the Emotion Discrimination task, eight variables yielded two components meeting Kaiser's criterion (Table 3): Discrimination Time (48.28% of variance) and Discrimination Correct (33.54% of variance).
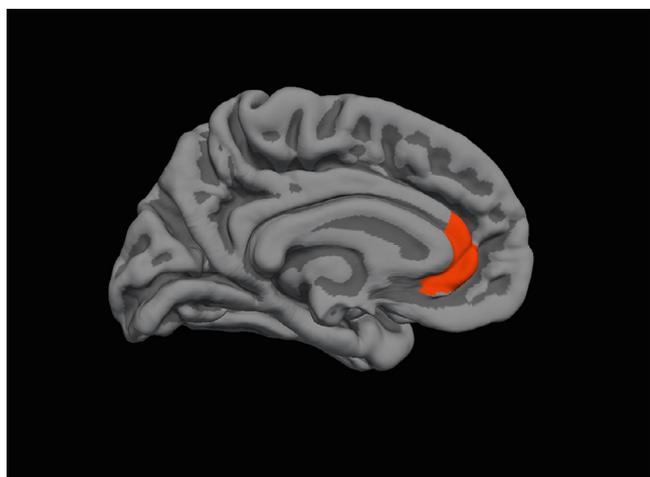
Table 4
Participant demographics.

	CAN Females (*n* = 8) % or *M* ± *SD* (range)	CNT Females (*n* = 19) % or *M* ± *SD* (range)	CAN Males (*n* = 12) % or *M* ± *SD* (range)	CNT Males (*n* = 16) % or *M* ± *SD* (range)
Race (% Caucasian)	37.5%	73.7%	83.3%	68.8%
Ethnicity (% Non-Hispanic)	62.5%	78.9%	91.7%	93.7%
Age (years)	21.4 ± 2.0 (19–24)	20.8 ± 2.5 (16–25)	22.0 ± 2.4 (18–26)	20.5 ± 3.2 (16–25)
Education (years)	14.1 ± 1.4 (12–16)	14.1 ± 1.9 (11–18)	14.4 ± 1.8 (11–18)	14.0 ± 3.0 (9–19)
WRAT-4 Word Reading (raw score)	58.8 ± 7.9 (41–67)	61.2 ± 4.2 (53–69)	62.0 ± 4.0 (55–69)	62.5 ± 3.8 (55–68)
Age of weekly cannabis use onset (years)	17.5 ± 0.9 (16–19)	–	17.6 ± 1.7 (15–20)	–
Lifetime cannabis use (uses)	797.8 ± 723.7 (101–2314)*	0.7 ± 1.2 (0–3)*	1339.8 ± 1550.0 (250–6000)*	0.6 ± 1.4 (0–5)*
Past year cannabis use (joints)	318.9 ± 301.3 (44.7–879.3)*	0.0 ± 0.0 (0–0)*	382.3 ± 361.4 (59–1394)*	.4 ± 1.3 (0–4.8)*
Number of cannabis uses/month in past 3 months	18.4 ± 12.1 (0–30)*	0.0 ± 0.0 (0–0)*	20.5 ± 10.0 (3–30)*	0.1 ± 0.3 (0–1)*
Length of cannabis abstinence (days)	26.0 ± 6.8 (22–40)	–	25.0 ± 9.3 (19–54)	–
Past year alcohol use (standard drinks)	339.6 ± 349.9 (0–883)*	59.4 ± 102.6 (0–450)*	433.5 ± 275.7 (70.5–897)*	115.5 ± 187.6 (0–698.5)*
Past year nicotine use (cigarettes)	46.4 ± 84.9 (0–232.3)*	.8 ± 2.8 (0–12)*	264.3 ± 448.2 (0–1088.5)*	0.1 ± 0.3 (0–1)*
Left Rostral Anterior Cingulate Cortex (rACC) volumes (mm³)	2449.0 ± 490.3 (1584–3180)	2777.6 ± 527.9 (1917–3658)	3125.9 ± 421.4 (2324–3741)	3257.3 ± 472.7 (2574–4322)

Note. WRAT-4 = Wide Range Achievement Test −4th edition Word Reading subtest. CAN = Cannabis-using. CNT = Non-using control.
 * Differences in CAN vs. CNT within gender = $p < 0.05$.

Fig. 1. Increased past year cannabis use significantly predicted smaller left rACC volumes [t (48) = −3.09, $beta$ = −0.33, p = 0.003, f^2 = 0.14; FDR corrected: p = 0.02].

3.3. Primary results

Greater past year cannabis use was significantly related to smaller left rACC volumes [t (48) = −3.09, $beta$ = −0.33, p = 0.003, f^2 = 0.14; FDR corrected: p = 0.02] (Figs. 1 and 2). Gender did not moderate this relationship. Within the left rACC regression model, the only covariate related to left rACC volumes was intracranial volume, which was positively associated with left rACC volume [t (48) = 5.16, $beta$ = 0.63, p = 0.000005].

Following FDR correction, past year cannabis use and cannabis × gender interaction were not significantly associated with volumes in any other regions.

3.4. Secondary results: brain-behavior relationships

Within cannabis users, smaller left rACC volumes were significantly associated with lower Discrimination Correct scores [r = 0.56,

p = 0.01; FDR-corrected: p = 0.02] (Fig. 3). No other affective measures were significantly associated with left rACC volumes within the cannabis-using group.

4. Discussion

To our knowledge, this is the first study to assess relationships between cannabis use, brain structure, and affective processing. We found that increased past year cannabis use was dose-dependently associated with smaller left rACC volumes in adolescents and young adults; gender did not significantly moderate this relationship. Notably, within cannabis-users, smaller left rACC volumes were significantly correlated with lower emotion discrimination accuracy.

Our finding that cannabis use was related to reduced left rACC volumes is consistent with other studies finding relationships between cannabis use and reduced volume and thickness in the ACC (Hill et al., 2016; Jacobus et al., 2014; Lisdahl et al., 2016; Rais et al., 2010; Rapp et al., 2013; Szeszko et al., 2007). Notably, many of the aforementioned studies (Rais et al., 2010; Rapp et al., 2013; Szeszko et al., 2007) included samples with psychiatric comorbidities (e.g., ADHD, psychosis). However, one study (Hill et al., 2016) that was conducted in participants without other psychopathology found that cannabinoid-1 (*CNR1*) receptor genotype moderates the relationship between level of cannabis exposure and reduced right ACC volumes. The current study builds upon the *right* ACC findings of Hill et al. (2016) by demonstrating a dose-dependent relationship between cannabis use and *left rostral* ACC. Therefore, though consistent with previous results of reduced ACC gray matter, the current study is novel in finding reduced rACC (but not cACC) volumes, in relation to cannabis use. This is consistent with literature supporting the rACC's involvement in emotional processing and the cACC's mediation of attention (Bush et al., 2000). Further, within the present study, smaller rACC volumes were only in the left hemisphere. Left unilateral reductions in the ACC are not a consistent finding in the literature (Hill et al., 2016; Lisdahl et al., 2016; Rapp et al., 2013; Szeszko et al., 2007) and thus, perhaps specific to the rostral portion of the ACC. The ACC itself is rich in CB1 receptors (Herkenham et al., 1990) and chronic cannabis use leads to downregulation of CB1 receptors in the cingulate cortex (Hirvonen et al., 2012). CB1
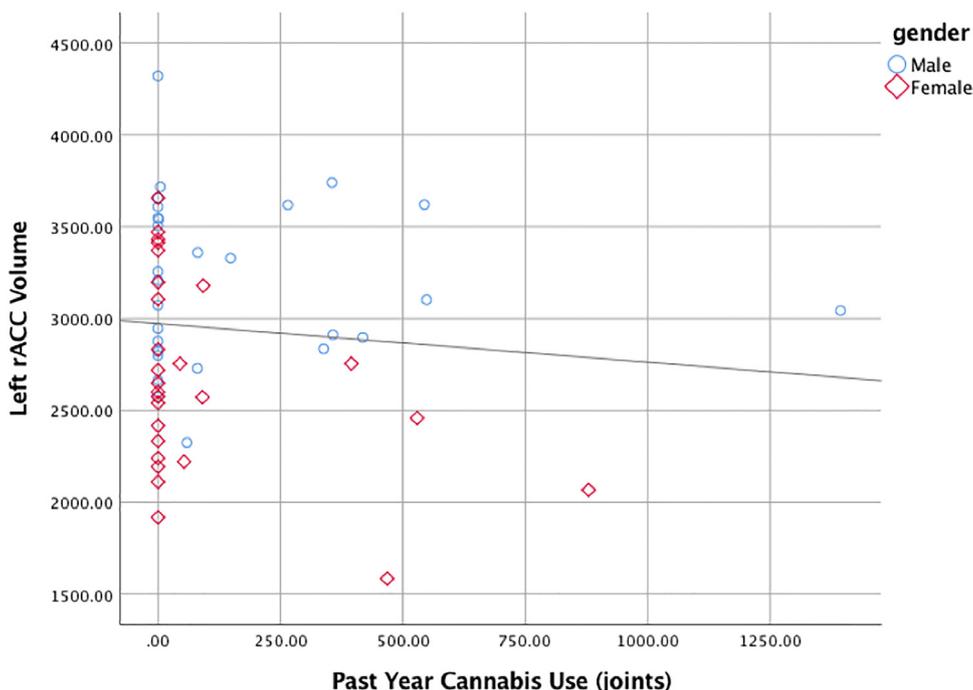

Fig. 2. Increased cannabis use significantly predicted smaller left rACC volumes [t (48) = −3.09, $beta$ = −0.33, p = 0.003, f^2 = 0.14; FDR corrected: p = 0.02].
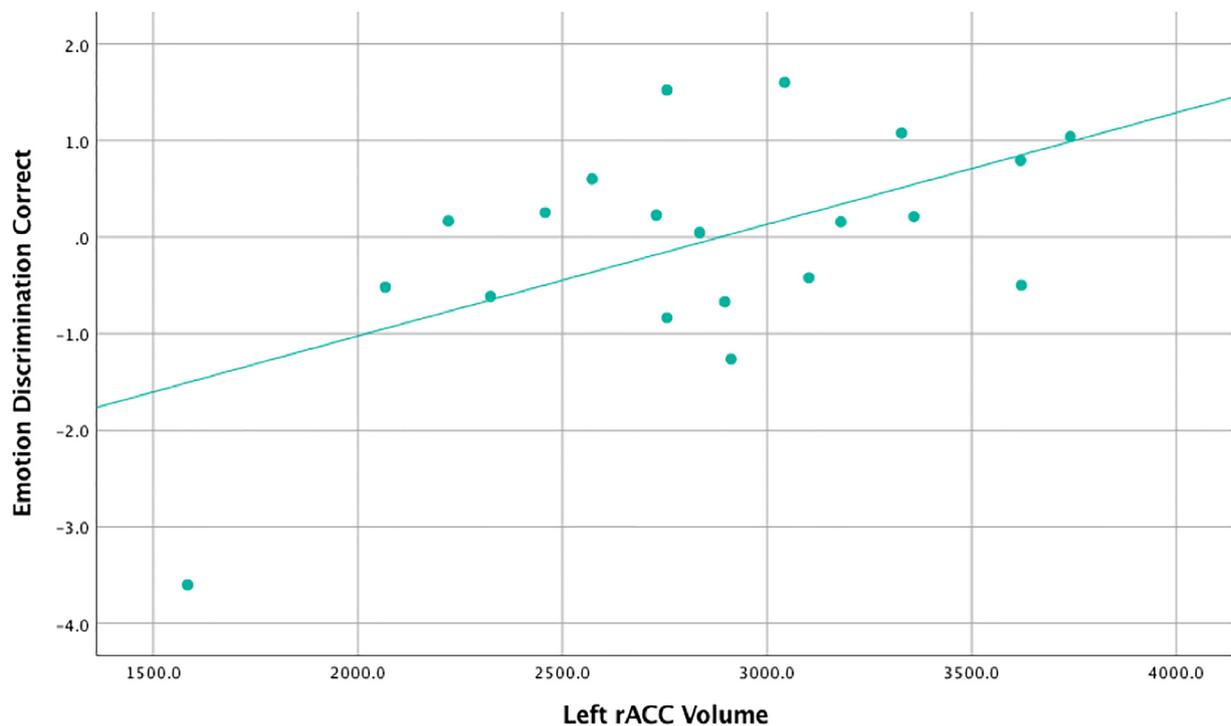
Fig. 3. Within the cannabis-using group, smaller left rACC volumes significantly predicted lower Discrimination Correct scores [$r = 0.56$, $p = 0.01$; FDR-corrected: $p = 0.02$].

downregulation may lead to reduced dendritic branching or neuronal atrophy, resulting in gray matter reductions (Lisdahl et al., 2014). The current study's findings suggest that rACC gray matter reductions may persist even after ≥ 3 weeks of abstinence. The present rACC structural findings also build upon studies showing relationships between both acute and chronic cannabis exposure and abnormal ACC activation and functional connectivity during emotion processing tasks (e.g., Gruber et al., 2009; Fusar-Poli et al., 2009a, 2010; Gorka et al., 2016; Wesley et al., 2016).

The ACC undergoes substantial structural and functional development during adolescence and young adulthood (Lichenstein et al., 2016; Pfeifer and Peake, 2012; Segalowitz and Dywan, 2009; Tamnes et al., 2013). Abnormal adolescent development of rACC structural and functional connectivity is associated with depression and anxiety (Clauss et al., 2014; Ho et al., 2017; Lichenstein et al., 2016; Swartz et al., 2014). Therefore, given the current study's findings, it is possible that adolescent cannabis use interrupts typical rACC development, increasing risk for affective disorders such as depression and anxiety. However, a longitudinal study would be necessary to confirm causal relationships between cannabis use, rACC structure, and development of affective disorders.

It is worth considering why Discrimination Correct was the only affective measure significantly related to the left rACC. Perhaps the rACC serves a crucial function in an aspect of the Emotion Discrimination task that is not present in the other tasks. For example, it is possible that the rACC is critical in comparing multiple emotional stimuli, such as faces (Munro et al., 2007). Additionally, research suggests a role for the rACC in shifting attention toward or away from emotional faces (Klumpp et al., 2012), which may be important if attending to multiple faces simultaneously. Another possibility is that the Emotion Discrimination task was more difficult (increased executive functioning load) compared to the Emotion Recognition and Emotional Acuity tasks, and thus more sensitive to rACC abnormalities. In functional neuroimaging studies of cannabis users, aberrant activation patterns often occur without differences in task performance (Lisdahl et al., 2014), suggesting that cannabis users may be able to

compensate by adjusting which regions are recruited for a particular task. Thus, perhaps due to simplicity of the Emotion Recognition and Emotional Acuity tasks, cannabis users in our sample were able to rely more heavily on other brain areas besides the rACC while completing those tasks, but not while completing the more demanding Emotion Discrimination task.

There are some additional important factors to consider when interpreting the current findings. Length of cannabis abstinence was much longer in our sample compared with many other studies (mean length of abstinence 25 days). In most studies, users are abstinent for an average of 2–3 days, and research suggests there may be significant cognitive recovery with abstinence (Hanson et al., 2010; Jacobus et al., 2012). Huijbregts et al. (2014) found that current cannabis users performed poorly on emotion recognition tasks (recognition and discrimination) relative to abstinent cannabis users and non-users. On the other hand, some structural and functional deficits persist in cannabis users after weeks of abstinence (Ganzer et al., 2016); one study that found emotion processing difficulties after three months of abstinence (Bayrakci et al., 2015). Therefore, the results of the current study suggest a mechanism (rACC structural differences) by which emotion processing deficits can persist in cannabis users. More research is needed to investigate specific emotion processing abilities (e.g., recognition vs. discrimination) in chronic cannabis use at varying lengths of abstinence. Another potential limitation is that age of cannabis use onset was not analyzed in the current study. Early age of onset in cannabis users has been related to poorer cognitive function as well as differences in brain activation and structure (Gruber et al., 2012, 2014; Pope et al., 2003; Sagar et al., 2015). However, it has been suggested that frequency of use over time, or dose-dependent effects such as those in the current analysis, likely have a greater impact on neurocognitive outcomes (Ganzer et al., 2016). Additionally, only one relationship (between cannabis and left rACC volumes) survived correction for multiple comparisons. As such, the other significant associations found may be spurious and must be interpreted with caution. Importantly, the current study only achieved 67% power at the effect size of the left rACC finding ($f^2 = 0.14$), and thus we cannot rule out Type I error (or

Type II error for the other brain regions). Greater statistical power in future studies would increase the likelihood of detecting interactions between gender and cannabis use. Finally, given the cross-sectional nature of this study, more work is needed to determine causal relationships.

We found an association between greater past year cannabis use and smaller left rACC volumes, even after ≥ 3 weeks of abstinence. Further, within abstinent cannabis users, smaller left rACC volumes were associated with poorer accuracy on an emotion discrimination task. Thus, chronic cannabis use during adolescence and young adulthood, a time of continued neurodevelopment (Casey et al., 2008), may have a negative, lasting impact on affective circuitry. This could result in difficulty discriminating subtle differences in emotions, which may negatively influence mood and emotional well-being (Phillips et al., 2003). Alternatively, those with smaller left rACC volumes and poorer emotion discrimination abilities may be more likely to use cannabis. This could be one mechanism underlying the comorbidity of cannabis use and psychiatric disorders (Gater et al., 1998; Rosen et al., 2006; Wittchen et al., 2007). Longitudinal work is needed to understand the causal relationships between substance use, comorbid disorders, gender, brain structure, and affective processing.

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Contributors

KEM was involved in data collection, developing the study concept, data processing, performing data analyses, interpreting the results, and writing the manuscript under KML's supervision. KML designed the study's methods and worked closely with KEM to develop the study concept, perform data analyses, interpret the results, and draft the manuscript. AMT was involved in data collection and data processing. MMK assisted in data collection, data processing, and preparation of the final manuscript.

Conflicts of interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.04.011.

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